Set Name Query side by side	Hit Count S	Set Name result set
DB=USPT,PGPB; PLUR=YES; OP=ADJ		
<u>L2</u> (encephalitis) same (viral or virus\$) same(alpha4 or 'vla-4')	2	<u>L2</u>
<u>L1</u> (encephalitis) same (viral or virus\$) and (alpha4 or 'vla-4')	41	<u>L1</u>

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VIRAL.USPT,PGPB.	47119
VIRALS.USPT,PGPB.	337
ALPHA4.USPT,PGPB.	148
ALPHA4S	0
VLA-4.USPT,PGPB.	599
VLA-4S	0
VIRUS\$	0
VIRUS.USPT,PGPB.	53937
VIRUSABILITY.USPT,PGPB.	2
((ENCEPHALITIS) SAME (VIRAL OR VIRUS\$) SAME(ALPHA4 OR 'VLA-4')).USPT,PGPB.	2

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L2: Entry 2 of 2

File: USPT

Nov 19, 2002

US-PAT-NO: 6482849

DOCUMENT-IDENTIFIER: US 6482849 B1

TITLE: Inhibitors of .alpha.4.beta.1 mediated cell adhesion

DATE-ISSUED: November 19, 2002

APPL-NO: 09/ 102584 [PALM]
DATE FILED: June 23, 1998

PARENT-CASE:

This application claims priority on provisional application Serial No. 60/050,515 filed on Jun. 23, 1997, the entire contents of which are hereby incorporated by reference.

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L2: Entry 2 of 2

File: USPT

Nov 19, 2002

US-PAT-NO: 6482849

DOCUMENT-IDENTIFIER: US 6482849 B1

TITLE: Inhibitors of .alpha.4.beta.1 mediated cell adhesion

DATE-ISSUED: November 19, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP	CODE	COUNTRY
Lobl; Thomas J.	Foster City	CA			
Teegarden; Bradley R.	San Diego	CA			
Polinsky; Alexander	San Diego	CA			
Rishton; Gilbert M.	Thousand Oaks	CA			
Yamagishi; Masafumi	Hyogo-ken				JP
Tanis; Steven	Kalamazoo	MI			
Fisher; Jed F.	Three Rivers	MI			
Thomas; Edward W.	Kalamazoo	MI			
Chrusciel; Robert A.	Portage	MI			

CLAIMS:

What is claimed is:

1. A compound of the formula (I): ##STR400##

wherein n is an integer of 1; R.sup.1 is a hydrogen atom or methyl group; R.sup.2 is a group of the formula: --CN, --COOH, --(C.sub.1-6 alkylene) OH, --CH.sub.2 O(C.sub.1-6 alkyl), --(C.sub.1-6 alkylene)COOH, --CH.sub.2 O(C.sub.1-6 alkylene)O(C.sub.1-6 alkyl), --CH.sub.2 O(C.sub.1-6 alkylene)COOH, --(C.sub.2-7 alkenylene) COOH, --CO(C.sub.1-6 alkylene) COOH, --CO(C.sub.2-7 alkenylene)COOH, --CO(C.sub.1-6 alkylene)O(C.sub.1-6 alkyl), --CO(C.sub.1-6 alkylene)CO(C.sub.1-6 alkyl), --CONH(C.sub.1-6 alkyl), --CONH(C.sub.1-6 alkyl), --CONH(C.sub.1-6 alkylene)COOH, --CONH.sub.2, --CONH(C.sub.3-7 cycloalkyl), ##STR401## --CONHOCH.sub.2 Ph, --CONH(C.sub.1-6 alkylene)CN, --COO(C.sub.1-6 alkyl), --CH.sub.2 O(C.sub.1-6 alkylene)CONH.sub.2, --CONH(C.sub.1-6 alkylene) CONH.sub.2, --CONHOH, --NHCOOCH.sub.2 Ph, ##STR402## R.sup.3 is a hydrogen atom or a methyl group; X is a methylene group or a group of the formula: --CO--; R.sup.4 is a hydrogen atom or a C.sub.1-6 alkyl group; R.sup.5 is a group of the formula: -- COOH or an ester or an amide thereof, -- (C.sub.1-6 alkylene) COOH or an ester or an amide thereof, -- (C.sub.1-7 alkylene) O(C.sub.1-6 alkyl), -- (C.sub.1-7 alkylene)OH, -- COO(C.sub.1-6 alkyl), -- CONH(C.sub.1-6 alkyl), or -- CONH.sub.2; R.sub.6 is a substituent of the formula: ##STR403## wherein, R.sup.7, which occurs one or more times and which may be the same or different in each occurrence, is --OH, --NO.sub.2, --NH.sub.2, --C.sub.1 -C.sub.5 alkyl, --F, --Cl, --Br, --I, --COOH, --COO(C.sub.1-6 alkyl), --O(C.sub.1 -C.sub.8 alkyl), --CONH(C.sub.1-6 alkylene)COOH, --OCH.sub.2 (C.sub.3 -C.sub.7 cycloalkyl) or a substituent of the formula ##STR404##

R.sup.8, which occurs one or more times and which may be the same or different in each occurrence, is --H, --OH, --NH.sub.2, --NO.sub.2, --C.sub.1 -C.sub.7 alkyl, --F, --Cl, --Br, --I, --CF.sub.3, phenyl, or --O(C.sub.1-6 alkyl); R.sup.9 is selected from a group of the formula: --H, --C.sub.1 -C.sub.5 alkyl, --C.sub.3 -C.sub.7 cycloalkyl, --(--C.sub.1 -C.sub.6 alkylene)aryl, aryl, where aryl is a substituent of the formula: ##STR405## R.sup.10, which occurs one or more times and which may be the same or different in each occurrence, is --H, --F, --Cl, --Br, --I, --NO.sub.2, --C.sub.1-6 alkyl or --O(C.sub.1-6 alkyl) with the proviso that R.sup.1 and R.sup.3 must be different and also with the proviso that when R.sup.2 or R.sup.6 is a moiety of the formula --COOH or contains a moiety of the formula --COOH, then a pharmaceutically acceptable ester or a pharmaceutically acceptable amide thereof are included, and also with the proviso that when R.sup.7 is the formula ##STR406## R.sup.9 is other than hydrogen; or

- a pharmaceutically acceptable salt thereof.
- 2. The compound according to claim 1, which is a compound of the formula (I-1): ##STR407##

wherein n, R.sup.1 through R.sup.6 and X are as defined above.

3. The compound according to claim 1, which is a compound of the formula (I-2): ##STR408##

wherein n, R.sup.1 through R.sup.4, R.sup.6 and X are as defined above and R.sup.5 is a group of the formula: --COOH, --(C.sub.1-6 alkylene)COOH, --(C.sub.1-7 alkylene)O(C.sub.1-6 alkyl), -(C.sub.1-7 alkylene)OH, --COO(C.sub.1-6 alkyl), --CONH(C.sub.1-6 alkyl), or --CONH.sub.2.

4. The compound according to claim 1, wherein R.sup.6 ##STR409##

wherein Y is a hydrogen atom or a chlorine atom.

- 5. The compound according to claim 1, wherein R.sup.2 is a group of the formula: --COOH or an ester or an amide thereof, --CONHCH.sub.2 COOH, --CONHOCH.sub.2 Ph or --CONHCH.sub.2 CONH.sub.2.
- 6. The compound according to claim 1, wherein R.sup.1 is --CH.sub.3, R.sup.2 is --COOH, --CONHCH.sub.2 COOH, CONHOCH.sub.2 Ph or --CONHCH.sub.2 CONH.sub.2, R.sup.3 is hydrogen, X is --CO--, R.sup.4 is hydrogen, R.sup.5 is --COOH, n is 1, and R.sup.6 is ##STR410## wherein R.sup.7 is ##STR411## wherein R.sup.8 is substituted 2 or 3 times and is --Cl.
- 7. The compound according to claim 1, wherein said compound is selected from the group consisting of Examples 10, 12, 13, 14, 16, 46, 53, 54, 61, 62, 63, 65, 75, 79, 81, 83, 85, 87, 89, 91, 92, 93, 95, 96, 97, 100, 102, 103, 104, 105, 106, 108, 110, 112, 114, 116, 118, 120, 121, 122, 124, 126, 128, 132, 134, 136, 141, 142, 144, 148, 150, 152, 153, 155, 161, 166, 170, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 211, 214, 216, 217, 219, 220, 221, 222, 223, 231, 232 and 236.
- 8. The compound according to claim 7, wherein said compound is selected from the group consisting of Examples 10, 12, 46, 53, 54, 61, 63, 65, 75, 81, 83, 87, 89, 91, 92, 93, 95, 97, 100, 102, 103, 104, 105, 106, 108, 110, 112, 114, 116, 118, 120, 121, 122, 124, 126, 128, 132, 134, 141, 142, 144, 148, 150, 152, 153, 161, 166, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 211, 214, 216, 217, 219, 220, 222, 223, 231, 232 and 236.
- 9. The compound according to claim 8, wherein said compound is selected from the group consisting of Examples 12, 54, 65, 81, 83, 87, 92, 93, 97, 100, 102, 103, 104, 106, 108, 110, 112, 114, 116, 148, 152, 166, 180, 181, 182, 183, 184, 211, 214, 216, 217, 219, 222, 223, 231, 232 and 236.
- 10. The compound according to claim 1, wherein said compound is selected from

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the group consisting of Examples 2, 10, 12, 13, 53, 54, 61, 63, 65, 75, 81, 83, 85, 86, 87, 89, 91, 92, 93, 95, 97, 100, 102, 103, 104, 105, 106, 108, 110, 112, 113, 114, 116, 118, 120, 121, 124, 126, 128, 132, 136, 137, 141, 142, 143, 144, 146, 148, 150, 152, 153, 155, 163, 166, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 211, 214, 216, 217, 219, 220, 221, 222, 223, 231, 232 and 236.
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- 11. The compound according to claim 10, wherein said compound is selected from the group consisting of Examples 10, 12, 54, 61, 63, 65, 75, 81, 83, 85, 87, 89, 91, 92, 93, 95, 97, 100, 102, 103, 104, 105, 106, 108, 110, 112, 114, 116, 120, 124, 126, 128, 132, 137, 142, 144, 146, 148, 152, 153, 166, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 211, 214, 216, 217, 219, 220, 222, 223, 232 and 236.
- 12. The compound according to claim 11, wherein said compound is selected from the group consisting of Examples 12, 54, 63, 83, 87, 91, 92, 93, 97, 100, 102, 103, 104, 106, 108, 110, 112, 116, 152, 166, 179, 180, 181, 182, 183, 184, 211, 214, 216, 217, 219, 223 and 232.
- 13. The compound according to claim 1, wherein said compound is selected from the group consisting of (1S-cis) -N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlo rophenyl) methyl] -L-tyrosine, (1S-cis) -N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichlo robenzoyl) amino] - L-phenylalanine, (1S-cis) -N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-O-[(2,6-dichlo rophenyl)methyl]-3-nitro-L-tyrosine, (1S-cis)-N-[(3-Carboxy-2,2,3-trimethylcyclopentyl)carbonyl]-4-[[(2,4,6-tri chlorophenyl) carbonyl] -amino] -L-phenylalanine, (1S-cis)-N-[[3-[[(2-Amino-2-oxoethyl)-amino]carbonyl]-2,2,3-trimethylcyclo pentyl]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine, $(1S-cis)-N-[\{3-[(Carboxymethyl)\,amino]\,carbonyl]-2,2,3-trimethylcyclopentyl$]carbonyl]-4-[(2,6-dichlorobenzoyl)amino]-L-phenylalanine, and (1S-cis) -N-[(3-Cyano-2,2,3-trimethylcyclopentyl)carbonyl]-4-[(2,6-dichloro benzoyl) amino] -L-phenylalanine.
- 14. A pharmaceutical composition comprising: a therapeutically effective amount of the compound as set forth in claim 1; and a pharmaceutically acceptable carrier or diluent.
- 15. A method for treating or preventing .alpha..sub.4.beta..sub.1 adhesion mediated conditions in a human which comprises administering to a patient an effective amount of the compound according to claim 1.
- 16. A method according to claim 15, wherein said condition is selected from the group consisting of rheumatoid arthritis, asthma, allergy conditions, allograft rejection, psoriasis, eczema, contact dermatitis and other skin inflammatory diseases, inflammatory and immunoinflammatory conditions including ophthalmic inflammatory conditions, inflammatory bowel diseases, atherosclerosis, and ulcerative colitis.
- 17. The compound according to claim 1, which is a compound as follows: $\#\$\mathsf{STR412}\#$

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L2: Entry 2 of 2

File: USPT

Nov 19, 2002

DOCUMENT-IDENTIFIER: US 6482849 B1

TITLE: Inhibitors of .alpha.4.beta.1 mediated cell adhesion

Detailed Description Text (575): VLA-4, a member of the .beta..sub.1 integrin family of adhesion molecules, is thought to play a critical role in several types of inflammatory disease processes by promoting leukocyte adhesion to vascular cell adhesion molecule (VCAM-1) and the CS-1 domain of fibronectin in extracellular tissue matrix (Elices M J, Osborn L, Takada Y, Crouse C, Luhowskyj S, Hemler M, Lobb R R. VCAM-1 on activated endothelium interacts with the leukocyte integrin VLA-4 at a site distinct from the VLA-4-fibronectin binding site. Cell; 60: 577-584, 1990, Humphries M J, Akiyama S K, Komoriya A, Olden K, Yamada K M. Identification of an alternatively-spliced site in human plasma fibronectin that mediates cell type-specific adhesion. J Cell Biol; 103: 2637-2647, 1986, Wayner E A, Garcia-Pardo A, Humphries M J, McDonald J A, Carter W G. Identification and characterization of the T lymphocyte adhesion receptor for an alternative cell attachment domain (CS-1) in plasma fibronectin. J Cell Biol; 109: 1321-1330, 1989, Guan J-L, Hynes R O. Lymphoid cells recognize an alternatively-spliced segment of fibronectin via the integrin .alpha..sub.1.beta..sub.1. Cell; 60: 53-61, 1990). Of the cell types expressing VLA-4, the major emphasis has been on eosinophils, lymphocytes, and monocytes. Validation of the role of VLA-4 has relied predominantly on the use of anti-VLA-4 antibodies which have been shown to suppress delayed-type hypersensitivity responses (Issekutz T B. Dual inhibition of VLA-4 and LFA-1 maximally inhibits cutaneous delayed-type hypersensitivity-induced inflammation. Am J Pathol; 143: 1286-1293, 1993, Scheynius A, Camp R L, Pure E. Reduced contact sensitivity reactions in mice treated with monoclonal antibodies to leukocyte function-associated molecule-1 and intercellular adhesion molecule-1. J Immunol; 150: 655-663, 1993, Ferguson T A, Kupper T S. Antigen-independent processes in antigen-specific immunity. J Immunol; 150: 1172-1182, 1993, Chisholm P L, Williams C A, Lobb R R. Monoclonal antibodies to the integrin .alpha.-4 subunit inhibit the murine contact hypersensitivity response. Eur J Immunol; 23: 682-688, 1993, Elices M J, Tamraz S, Tollefson V, Vollger L W. The integrin VLA-4 mediates leukocyte recruitment to skin inflammatory sites in vivo. Clin Exp Rheumatol; 11 (Suppl 8) S77-80), 1993, experimental allergic encephalomyelitis (Yednock T A, Cannon C, Fritz L C, Sanchez-Madrid F, Steinman L M, Karin N. Prevention of experimental autoimmune encephalomyelitis by antibodies against .alpha..sub.4.beta..sub.1 integrin. Nature; 356: 63-66, 1992, Canella B, Raine C S. The VCAM-1/VLA-4 pathway is involved in chronic lesion expression in multiple sclerosis (MS). J Neuropathol Exp Neurol; 52: 311, 1993), HIV-induced encephalitis (Sasseville V G, Newman W, Brodie S J, Hesterberg P, Pauley D, Ringler D J. Monocyte adhesion to endothelium in simian immunodeficiency virus-induced AIDS encephalitis is mediated by vascular cell adhesion molecule-1/.alpha..sub.4.beta..sub.1 integrin reactions. Am J Pathol; 144: 27-40, 1994), pulmonary inflammation and airway hyperreactivity in asthma (Abraham W M, Sielczak M W, Ahmed A, Cortes A, Lauredo I T, Kim J. Pepinsky, B, et al. .alpha..sub.4 -integrins mediate antigen-induced late bronchial responses and prolonged airway hyerresponsiveness in sheep. J Clin Invest; 93: 776-787, 1994, Pretolani M, Ruffie C, Roberto LapaeSilva J, Joseph D, Lobb R R, Vargaftig B B. Antibody to very late activation antigen 4 prevents antigen-induced bronchial hyperreactivity and cellular infiltration in the guinea-piq airways. J Exp Med; 180: 795-805, 1994), experimental models of autoimmune-mediated diabetes (Yang X-D, Karin N, Tisch R. Steinman L, McDevitt H O. Inhibition of insulitis and prevention of

diabetes in non-obese diabetic mice by blocking L-selectin and very late antigen 4 adhesion receptors. Proc Natl Acad Sci USA; 90: 10494-10498, 1993, Burkly L C, Jakubowski A, Hattori M. Protection against adoptive transfer of autoimmune diabetes medicated through very late antigen-4 integrin. Diabetes; 43: 529-534, 1994), and experimental colitis (Podolsky D K, Lobb R, King N, Benjamin C D, Pepinsky B, Sehgal P, et al. Attentuation of colitis in the cotton-top Tamarin by anti-.alpha.4 integrin monoclonal antibody. J Clin Invest; 92: 372-380, 1993). Since eosinophils represent a major component of the inflammatory cell influx in asthmatic lung tissue we developed a simple acute inflammatory model of VLA-4 integrin-dependent eosinophil infiltration which could be used to identify VLA-4 antagonists; such compounds would be of potential value in the treatment of asthma as well as other diseases in which VLA-4 played a role.

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L2: Entry 1 of 2

File: PGPB

Nov 14, 2002

DOCUMENT-IDENTIFIER: US 20020168370 A1

TITLE: Methods and compositions for treating secondary tissue damage and other

inflammatory conditions and disorders

Detail Description Paragraph (349):

[0411] Tyor et al. (1993) A model of human immunodeficiency virus encephalitis in scid mice, Proc Natl Acad Sci USA 90:8658-62, provides an animal model of HIV-associated dementia complex to aid in development of treatments therefor. Mice with severe combined immunodeficiency (scid mice), which accept xenografts without rejection, were intracerebrally inoculated with human peripheral blood mononuclear cells and HIV. One to 4 weeks after inoculation, the brains of these mice contained human macrophages (some of which were HIV p24 antigen positive), occasional multinucleated cells, and striking gliosis by immunocytochemical staining. Human macrophages also were frequently positive for tumor necrosis factor type alpha and occasionally for interleukin 1 and VLA-4. Cultures of these brains for HIV were positive. Generally, human macrophages were not present in the brains of control mice, nor was significant gliosis, and HIV was not recovered from mice that received HIV only intracerebrally. Pathologically, this model of HIV encephalitis in scid mice resembles HIV encephalitis in humans and the data suggest that the activation of macrophages by infection with HIV results in their accumulation and persistence in brain and in the development of gliosis. This model of HIV encephalitis provides insights into the pathogenesis and treatment of this disorder.

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7. 20020197679. 13 Mar 02. 26 Dec 02. Novel nucleic acids and polypeptides. Tang, Y. Tom, et al. 435/69.1; 435/183 435/320.1 435/325 530/350 536/23.2 C12P021/02 C12N005/06 C07H021/04 C12N009/00 C07K014/435.
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☐ 19. 6503713. 04 Oct 00; 07 Jan 03. Methods for identifying RNA binding compounds. Rana; Tariq M. 435/6; 435/5 435/7.1 435/7.2 514/44 530/300 536/22.1 536/23.1 536/24.3. C12Q001/68 C07H019/00 C07H021/00 A01N043/04.
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25. <u>6482618</u> . 04 Apr 02; 19 Nov 02. Self-enhancing, pharmacologically controllable expression systems. Mueller; Rolf, et al. 435/91.41; 435/320.1 435/325 536/23.4 536/24.1. C12N015/66.
26. <u>6479492</u> . 21 Jan 00; 12 Nov 02. Compounds which inhibit leukocyte adhesion mediated by <u>VLA-4</u> . Konradi; Andrei W., et al. 514/241; 514/245 544/180 544/194 544/204 544/217 544/220. A61K031/53 C07D251/00 C07D251/48 C07D251/49.
27. 6465513. 21 Jan 00; 15 Oct 02. Multicyclic compounds which inhibit leukocyte adhesion mediated by <u>VLA-4</u> . Grant; Francine S., et al. 514/529; 514/18 514/19 514/255.01 562/507. A01N037/00 C07C229/00.
28. <u>6436904</u> . 21 Jan 00; 20 Aug 02. Compounds which inhibit leukocyte adhesion mediated by <u>VLA-4</u> . Ashwell; Susan, et al. 514/19; 546/208 546/210 548/253 548/542. A61K038/05 C07K005/06.
29. 6423688. 31 Jul 98; 23 Jul 02. Dipeptide and related compounds which inhibit leukocyte adhesion mediated by VLA-4. Thorsett; Eugene D., et al. 514/19; 514/18 530/331 548/535. C07K005/078.
30. <u>6410781</u> . 28 Feb 00; 25 Jun 02alphaaminoacetic acid derivativesalpha.4.beta.7 receptor antagonists. Konradi; Andrei W., et al. 560/133; 544/59 546/333 560/132. C07C271/44 A61K031/27.
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41. <u>5596090</u>. 12 Oct 93; 21 Jan 97. Antisense oligonucleotides directed against human VCAM-1 RNA. Hoke; Glenn D., et al. 536/24.5; 435/6 536/23.1 536/24.1 536/24.3 536/24.31. C07H021/04 A61K031/70.

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Term	Documents
ENCEPHALITIS.USPT,PGPB.	3762
ENCEPHALITI.USPT,PGPB.	1
VIRAL.USPT,PGPB.	47119
VIRALS.USPT,PGPB.	337
ALPHA4.USPT,PGPB.	148
ALPHA4S	0
VLA-4.USPT,PGPB.	599
VLA-4S	0
VIRUS\$	0
VIRUS.USPT,PGPB.	53937
VIRUSABILITY.USPT,PGPB.	2
((ENCEPHALITIS) SAME (VIRAL OR VIRUS\$) AND (ALPHA4 OR 'VLA-4')).USPT,PGPB.	41

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((ENCEPHALITIS) SAME (VIRAL OR VIRUS\$) SAME(ALPHA4 OR 'VLA-4')).USPT,PGPB.	2

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<u>L2</u>	(encephalitis) same (viral or virus\$) same(alpha4 or 'vla-4')	2	<u>L2</u>
<u>L1</u>	(encephalitis) same (viral or virus\$) and (alpha4 or 'vla-4')	41	<u>L1</u>

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VIRAL.USPT,PGPB.	47119
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